1: Anesth Analg 1997 Mar;84(3):479-83 Related Articles, Links

Hemofiltration during cardiopulmonary bypass: the effect on anti-Xa and anti-IIa heparin activity.

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Previous studies have demonstrated that heparin concentrations during cardiopulmonary bypass (CPB) may vary considerably, which may be related to variability in redistribution, cellular and plasma protein binding, and clearance of heparin. The purpose of this study was to determine whether hemofiltration removes lower molecular weight fractions of heparin from plasma and thus contributes to variability of blood levels of heparin. Twenty patients undergoing cardiac surgery with CPB were enrolled in this study after informed consent was obtained. The study was subdivided into two phases. The first 10 patients were enrolled in Phase I, which was designed to determine whether hemofiltration removes lower molecular weight fractions of heparin from blood. Blood specimens obtained from the inflow line and outflow lines of the hemofiltration unit were used to measure complete blood counts (CBC) and plasma heparin activity by anti-Xa and anti-IIa assays. Phase II was designed to evaluate the effect of hemofiltration on circulating plasma heparin activity. In Phase II, blood specimens were obtained from 10 patients via the arterial cannula of the extracorporeal circuit prior to and after hemofiltration for measurements of CBCs, anti-Xa plasma heparin, as well as whole blood heparin concentration using an automated protamine titration assay (Hepcon instrument, Medtronic Inc., Parker, CO). Ultrafiltrate and reservoir volumes were measured in both phases of the study. Hemofiltration did not remove lower (anti-Xa measurable) molecular weight heparin, but it resulted in a considerable increase in heparin activity in the outflow line, as measured by both anti-Xa and anti-IIa assays. The plasma anti-Xa heparin activity obtained after hemofiltration (5 +/- 1.8 U/mL) was substantially ($P = 0.003$) greater than heparin activity obtained prior to hemofiltration (3.9 +/- 1.7 U/mL). The increase in heparin activity with hemofiltration was directly related to ultrafiltrate volume ($r = 0.63$, $P < 0.0001$) and hematocrit ($r = 0.73$, $P < 0.0001$). Hemofiltration increases heparin concentration and may contribute to variability in heparin activity during CPB. Point-of-care heparin concentration methods would allow identification of the anticipated rise in heparin concentration, with the apparent clinical implication of a reduced need for supplemental heparin to maintain a target whole blood heparin

concentration.

Publication Types:
- Clinical Trial

PMID: 9052286 [PubMed - indexed for MEDLINE]

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1: Thromb Res 1990 Feb 15;57(4):585-92 Related Articles, Links

In vitro effect on Heptest of low molecular weight heparin fractions and preparations with various anti-IIa and anti-Xa activities.

Bara L, Mardiguian J, Samama M.

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The Heptest heparin assay has recently been introduced, and evaluated for the laboratory monitoring of patients receiving low molecular weight heparins (LMWH). The aim of the present study was to elucidate the relative role on the Heptest assay of the anti-factors Xa and IIa activities present in the three types of compounds that possess: 1. exclusively anti-Xa activity (LF1: LMWH fractions with MW ranging from 1,200 to 4,200 D.); 2. both anti-Xa and anti-IIa activities (LF2 with MW from 4,800 to 12,000 D.); 3. exclusive anti-IIa activity (Hirudin and Dermatan Sulfate). All compounds studied demonstrated dose-dependent activities in both amidolytic and clotting assays. The LF2 in contrast to the LF1, additionally enhanced the clotting times of Heptest. This enhancement was shown to be due to the anti-Factor IIa activity of the agents. Heptest does not exclusively reflect Anti-Xa activity since it is influenced by agents containing exclusive anti-IIa activity like Hirudin and Dermatan Sulfate. At low concentrations of LF2, Heptest measures predominantly the anti-factor Xa activity while at higher concentrations it is influenced by the combined activity of anti-factor Xa and anti-factor IIa. However, Heptest sensitivity to anti-factor IIa is significantly lower than for anti-Xa activity.

PMID: 2158152 [PubMed - indexed for MEDLINE]

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1: Haemostasis 1988;18 Suppl 3:64-8 Related Articles, Links

Anti-IIa and anti-Xa plasma activities after subcutaneous low-dose application of low-molecular-weight heparins to rabbits.

Harbauer G, Kettenring P.

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Low-molecular-weight heparin (LMWH) derivatives differ among one another and from unfractioned heparin (UFH) in their half-life as well as in their mode of action. Our aim was to find out, whether the plasma activity levels and their time course after subcutaneous low-dose application of LMWH or UFH in the experimental rabbit are comparable to those in humans. Fairly reasonable standard curves for each LMWH preparation were obtained by using geometrical dilution series of spiked rabbit pool plasma and by applying the methods of Bartl et al. (anti-IIa) and Holmer et al. (anti-Xa). The latter method was slightly modified in order to achieve discernable photometric absorptions for activity levels less than 0.05 U/ml. Rabbits under intravenous general anesthesia received an anterior neck incision. The right external jugular vein was dissected free. A catheter was inserted, advanced into the upper caval vein and kept patent by continuous infusion of 10 ml/h of normal saline. Blood samples of 4 ml were collected in syringes containing 1 ml sodium citrate, before and 1, 2, 4 and 8 h after subcutaneous injection of a LMWH derivative or UFH. The samples were centrifuged and frozen to -30 degrees C. For the estimation of heparin-like anti-IIa and anti-Xa activities the samples were thawed and treated in the same manner as the samples from which the standard curves had been derived.(ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 2840376 [PubMed - indexed for MEDLINE]

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1: Thromb Res 2003 Jan 25;109(2-3):109-17 Related Articles, Links

SCIENCE DIRECT FULL TEXT ARTICLE

Comparative study of the pharmacokinetic profiles of two LMWHs-bemiparin (3500 IU, anti-Xa) and tinzaparin (4500 IU, anti-Xa)-administered subcutaneously to healthy male volunteers.

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Pharmacokinetic profiles of bemiparin (3500 IU, anti-Xa) and tinzaparin (4500 IU, anti-Xa) administered subcutaneously to 12 healthy male volunteers were compared in a monocentric study. Each of the 12 subjects underwent successively the two low-molecular-weight heparin (LMWH) preparations in a randomised order and was considered as its own control. Anti-Xa activity, free and total tissue factor pathway inhibitor (TFPI), and thromboplastin-thrombomodulin-mediated time were determined as main variables. Activated partial thromboplastin time (APTT), thrombin clotting time, and anti-IIa activity were also determined. Bemiparin (3500 IU, anti-Xa) exerts a significantly more rapid, more potent, and more prolonged anti-Xa activity than tinzaparin (4500 IU, anti-Xa). The plasma level increase for free and total TFPI is significantly lower with bemiparin than with tinzaparin. Free and total TFPI peak levels occur earlier than anti-Xa activity peak levels for both LMWH preparations, but no statistical difference appeared between the two preparations for TFPI T(max). No significant effect was observed for both preparations for thromboplastin-thrombomodulin-mediated time. Subcutaneous injection of bemiparin exerts only minimal anti-IIa activity and does not prolong thrombin time, whereas tinzaparin elicits significant anti-IIa activity and prolongs thrombin clotting time. Bemiparin exerts a significantly lower prolongation of APTT than tinzaparin. No difference was observed for APTT prolongation T(max) between the two preparations. Globally, the overall tolerability of both formulations revealed no relevant adverse effects. In conclusion, bemiparin and tinzaparin are not bioequivalent. Bemiparin exerts an important and more prolonged anti-Xa activity in comparison with tinzaparin. An original finding of this study is the difference observed between the two formulations for free TFPI release.

PMID: 12706639 [PubMed - in process]

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1: Thromb Haemost 2000 Nov;84(5):800-4 Related Articles, Links

Elderly patients treated with tinzaparin (Innohep) administered once daily (175 anti-Xa IU/kg): anti-Xa and anti-IIa activities over 10 days.

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Since low molecular weight heparins (LMWH) are partly eliminated by renal excretion, their pharmacodynamic profile may be modified in very elderly patients with age-related renal impairment. The aim of this prospective study was to determine whether tinzaparin (Innohep) 175 anti-Xa IU/kg administered subcutaneously once daily over 10 days does accumulate in hospital patients greater than 70 years of age. Plasma anti-Xa and anti-IIa amidolytic levels and APTT were determined prior to the first injection (day 0), and then, at peak level i.e. 5 h after the second injection (day 2) and subsequently on days 5, 7 and 10. Thirty consecutive inpatients (6 men, 24 women) requiring LMWHs at a curative dose for acute thromboembolic disease were included. Patients' characteristics (mean +/- SD) were: age 87.0+/-5.9 years (range 71-96), body weight 62.7+/-14.6 kg (range 38-90) and creatinine clearance 40.6+/-15.3 mL/min (range 20-72). The mean actual dose of tinzaparin delivered was 174.8 anti-Xa IU/kg. Since no patient had an anti-Xa activity above 1.5 IU/mL, the dose of tinzaparin remained fixed over 10 days. Anti-Xa and anti-IIa peak levels measured on day 2 were 0.66+/-0.20 IU/mL (range 0.26-1.04) and 0.33+/-0.10 IU/mL (range 0.18-0.55), respectively. Ex vivo anti-Xa/anti-IIa ratios were close to 2.1. APTT ratios (patient/control) were strongly correlated with anti-IIa activity ($p < 0.01$). There was no progressive increase of the anti-Xa and anti-IIa activities after repeated administration of tinzaparin over the 10 day treatment period. No correlation was found between anti-Xa and anti-IIa activities and age, weight, or creatinine clearance. No major bleeding occurred during the study and only one minor haematoma at the injection site was reported. No thrombo-embolic complication or death occurred. Tinzaparin may thus be administered safely at a treatment dose (175 anti-Xa IU/kg) in older patients with age-related renal impairment. Neither dose adjustment, nor serial anti-Xa activity monitoring seems to be required in patients with creatinine clearance above 20 mL/min during the first ten day treatment.

PMID: 11127859 [PubMed - indexed for MEDLINE]

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1: Br J Haematol 1999 Feb;104(2):230-40 Related Articles, Links

Occurrence of thrombosis and haemorrhage, relationship with anti-Xa, anti-IIa activities, and D-dimer plasma levels in patients receiving a low molecular weight heparin, enoxaparin or tinzaparin, to prevent deep vein thrombosis after hip surgery.

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Studies in experimental animal models and in patients receiving low molecular weight heparin (LMWH) to prevent thromboembolic events after surgery have not demonstrated a clear relationship between anti-Xa and anti-IIa activities in plasma and either bleeding or prevention of thrombosis. The relationship between these clinical outcomes and ex vivo anti-Xa and anti-IIa activities, activated partial thromboplastin time (APTT) and D-dimers were evaluated in 440 patients undergoing total hip replacement and given prophylaxis once daily with a LMWH (tinzaparin or enoxaparin) in a multicentre double-blind randomized study. 221 patients received 4500 anti-Xa IU of tinzaparin; 219 patients received 40 mg (4000 anti-Xa IU) of enoxaparin. Both regimens were administered subcutaneously once daily. Blood samples for anti-IIa, anti-Xa, D-dimers levels and APTT were taken at baseline, on day 1, day 5 and on the day of discharge (days 8-14) and clinical assessments were performed dafly until day 14. All patients had bilateral venography between days 8 and 14. All coagulation tests were performed in central laboratories. A significant correlation was observed between anti-IIa activity and anti-Xa activity and the dose of each LMWH injected. The anti-Xa activity was significantly higher with enoxaparin and the anti-IIa activity was significantly higher with tinzaparin. No clear relationship between these two activities and the clinical outcomes was observed. This was also true with regards to APTT. Before and after surgery, D-dimers were significantly higher in patients with deep vein thrombosis (DVT) than in those without DVT but had no predictive value. Interestingly, a significant post-operative increase of D-dimers persisted in both groups of patients during the whole observation period, possibly suggesting that a longer duration of prophylactic treatment may be appropriate.

Publication Types:
- Clinical Trial
- Multicenter Study

- Randomized Controlled Trial

PMID: 10050702 [PubMed - indexed for MEDLINE]

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